Cerebellar Cortical Lamination and Foliation Require Cyclin A2.

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Public Summary:

Scientific Abstract:
The mammalian genome encodes two A-type cyclins, which are considered potentially redundant yet essential regulators of the cell cycle. Here, we tested requirements for cyclin A1 and cyclin A2 function in cerebellar development. Compound conditional loss of cyclin A1/A2 in neural progenitors resulted in severe cerebellar hypoplasia, decreased proliferation of cerebellar granule neuron progenitors (CGNP), and Purkinje (PC) neuron dyslamination. Deletion of cyclin A2 alone showed an identical phenotype, demonstrating that cyclin A1 does not compensate for cyclin A2 loss in neural progenitors. Cyclin A2 loss lead to increased apoptosis at early embryonic time points but not at post-natal time points. In contrast, neural progenitors of the VZ/SVZ did not undergo increased apoptosis, indicating that VZ/SVZ-derived and rhombic lip-derived progenitor cells show differential requirements to cyclin A2. Conditional knockout of cyclin A2 or the SHH proliferative target Nmyc in CGNP also resulted in PC neuron dyslamination. Although cyclin E1 has been reported to compensate for cyclin A2 function in fibroblasts and is upregulated in cyclin A2 null cerebella, cyclin E1 expression was unable to compensate for loss-of cyclin A2 function.